Turner-Stokes L, Nair A et al. Multi-disciplinary rehabilitation for acquired brain injury in adults of working age. Cochrane Database of Systematic Reviews 2005, Issue 3, Art. No CD004170.

Design: Systematic review of randomized trials, quasi-randomized trials, and quasi-experimental studies

PICOS:

- **P**atients: adults of working age (mean age between 18 and 65) with acquired brain injury due to TBI, stroke, diffuse brain injury (hypoxia, hypoglycemia, etc), or mixed etiologies
- **I**nterventions: Any intervention delivered by two or more disciplines in a coordinated effort to reduce disability or handicap as a result of disease or injury
- **C**omparison/controls: routinely available local services or lower levels of multidisciplinary intervention
- **O**utcomes: two broad categories of outcome: (1), impairment and disability (residual symptoms, amnesia, level of mobility, cognitive functioning, activities of daily living--ADL) and (2), level of participation (previously called handicap: i.e., return to work) and quality of life (social integration, level of anxiety and depression, psychosocial adjustment)
- **S**tudy types: both randomized clinical trials and quasi-experimental designs, provided that the latter had a large element of chance in which kind of service was provided to the patient

Study type and selection:

- Databases included MEDLINE, EMBASE, the Cochrane Library, Web of Science, National Research register 2007, clinicaltrials.gov, and RehabTrials.org
- Additional trials were identified from reference lists and through consultation with colleagues and trialists
- At least two authors reviewed studies for eligibility and for quality using a method with 11 internal validity items, 6 descriptive items, and 2 statistical items
- Disagreements between article raters were resolved through discussion or through consultation with a third author
- The current review was an update of a review first published in 2005, and certified as up to date in 2008 without revisions to the conclusions

Results:

- 16 studies were selected for analysis; 10 studied TBI, 4 studied stroke, and 1 studied mixed acquired brain injury; 1 study was later excluded for having too high an attrition rate
- Trials were divided into two broad categories
    - One category (n=5) enrolled all patients presenting acutely with TBI, which included patients with milder forms of ambulatory TBI; the

interventions were aimed at improving participation (social integration and return to work)

- One category (n=11) enrolled patients who were already referred for rehabilitation services, and had greater levels of motor impairment and dependence in ADL; the interventions were mostly aimed at reducing disability
    - 2 of these trials assessed outpatient rehabilitation, 3 assessed benefits of community-based multidisciplinary programs, 2 assessed specialist inpatient rehabilitation, and 4 compared low intensity with higher intensity of treatment
- Because studies used different outcomes measured at different time intervals using different interventions, there was insufficient homogeneity to allow pooling of data for meta-analysis
- The 5 trials which looked at milder ambulatory TBI recruited 1258 patients; the general conclusion was that multidisciplinary intervention in milder TBI was not effective
    - One post-hoc analysis suggested that patients who had had one hour or more of post-traumatic amnesia did benefit from treatment, having gains in ADL participation
- Community-based coordinated multidisciplinary rehabilitation was examined in 2 studies of TBI in more severely affected patients; one good single blind RCT showed that the treatment group had improvement in ADL as assessed by the Barthel index, and a lesser quality unblinded trial suffered from logistic difficulties (many patients never receiving the assigned treatment), and was underpowered for showing a clinically important effect
    - The Cochrane reviewers interpreted this as ‘limited evidence’ that multidisciplinary treatment can improve functional outcomes for TBI patients with significant functional impairment
- Specialist inpatient rehabilitation was assessed in 2 trials, 1 for TBI and 1 for stroke; the TBI study had methodological problems which compromised its results, but the unblinded stroke study reported greater functional gains in the treatment group than in the control group
- Both of the specialist inpatient rehabilitation (1 TBI, 1 stroke) studies were underpowered and of low quality
- The 4 studies comparing high and low intensity rehabilitation (1 stroke, 2 TBI, and 1 mixed stroke, TBI, and MS) collectively supported a “strong” evidence statement that more intensive rehabilitation is associated with earlier functional gains once patients are able to participate; the same studies did not examine whether the interventions were cost effective down the line

Authors' conclusions:

- Multidisciplinary rehabilitation by expert neurological rehabilitation services improves outcomes after acute brain injury in working-age adults
- TBI patients with milder injuries not leading to hospitalization, or with post-traumatic amnesia lasting less than 30 minutes, are likely to recover without specialist care
- The key features of a successful program are that it includes a multi-specialty team in which all members have relevant expertise, it includes education for relatives as well as for patients, that it is located in a specific geographic base, and that it uses protocols based on evidence when possible
- There is limited evidence from many of the studies which are poor in quality when judged using the quality-of-evidence tool commonly used in Cochrane reviews
- Many special difficulties occur in assessing the evidence supporting complex interventions for conditions like TBI
    - RCTs are well-suited for single easily identified interventions, such as drugs or procedures
    - Rehabilitation is complicated (multi-factorial) intervention which is undertaken in a mathematically complex situation, where many interrelated factors interact, yielding relationships which may be non-linear and unpredictable
    - In studies of brain injury rehabilitation, patient numbers are frequently too few to adequately power a robust analysis; many sources of heterogeneity are simultaneously operating, and these are relevant to measuring the outcomes of treatment
    - The resources required for randomization of complex interventions to systems of care are greater than those required to randomize them to specific medications
    - The length of time over which the interventions exert an effect may be longer than the funding for the research project
    - Recruitment and retention of participants can be difficult; patients randomized to the control arm may be disappointed and drop out of the study, leading to high attrition in that arm of the study
    - Many studies need to be multi-centered in order to have sufficient numbers of participants; however, different centers often do things very differently, creating additional heterogeneity
    - The outcome measures may not be as homogeneous as often thought; for example, even consistently applied instruments may behave differently in different cultures and settings
    - Overall scores on global outcome scales may be insensitive to changes in attaining specific treatment goals, making them unlikely to reflect the true benefits of the intervention

Comments:

- The reasons for not pooling data for meta-analysis are well reasoned and persuasive

- The search strategy is clear enough to be reproducible; for a systematic review of the literature, this is more important than whether a meta-analysis was done
- Some interventions appear to be difficult to classify as multidisciplinary
    - For example, in Table 4, Wade 1997 described the intervention as "telephone follow-up at 7-10 days with advice and referral as required;
    - In Table 5, Skiel 2001 has the study intervention as enhanced intensity, described as "intervention by experienced rehabilitation professional, (nurse in one center, occupational therapist in the other); the control intervention is "Routine: multidisciplinary rehab"
    - One minor typographical error occurs in Table 4; for Paniak 1998 and 2000, the difference in means for vocational status at baseline is 0.8, but the true difference in means is 3.7; manual calculation of the t-test still confirms that the difference is not significant
- The discussion section is lucid and summarizes clearly many of the reasons that evidence of treatment effectiveness for TBI interventions proves elusive
- One of the references (Tennant 2004) cited in support of the statement that cultural differences can affect the analysis of disability discusses item response theory, which may be more sensitive to change than raw scores on some commonly used outcome measures; if true, this could suggest ways in which the statistical analyses of future studies could be made more sophisticated
- Overall, the review makes a credible case that many studies of TBI intervention are likely to fail to detect actual benefits (underpowered, high degrees of heterogeneity which have the effect of unmeasured confounding, statistical analyses which are insensitive to functional targeted change)

Assessment: adequate for good evidence that multidisciplinary rehabilitation of TBI patients who required hospital admission are likely to benefit functionally and symptomatically; adequate for good evidence that mild TBI without post-traumatic amnesia does not require routine rehabilitation

Reference:

Tennant A, Penta M, et al. Assessing and Adjusting for Cross-Cultural Validity of Impairment and Activity Limitation Scales Through Differential Item Functioning within the Framework of the Rasch Model. Medical Care 2004;42 suppl 1:I37-I48.